Comprehensive Analysis of the High Entropy-Production Zone (HEZ) and Marangoni-Driven Convection in Corneal Stromal Dynamics
A New Perspective on Corneal Thermodynamics and the Maintenance of Homeostasis

The human cornea is a highly specialized, metabolically active, yet avascular tissue that preserves optical transparency under tightly regulated physiological conditions. To maintain this structural order and transparency, the cornea may be viewed as a non-equilibrium open system operating far from thermodynamic equilibrium. Traditionally, the mechanisms underlying corneal hydration control and transparency have been explained primarily through the classical “pump-leak mechanism.” In this well-established framework, active ion transport mediated by Na^+/K^+-ATPase pumps on the basolateral side of corneal endothelial cells counterbalances the passive influx of aqueous humor into the stroma driven by the swelling pressure of stromal glycosaminoglycans (GAGs), thereby helping maintain corneal water content within a narrow physiological range of approximately 78%. Although the pump-leak hypothesis has long provided a valuable foundation in ophthalmic biophysics, it may not fully account for the complex, large-scale horizontal fluid dynamics observed in vivo. Conventional models often regard the corneal stroma as a relatively homogeneous and passive medium. In reality, however, the corneal stroma shows marked structural and anatomical heterogeneity along the depth axis. Previous studies using microfocus X-ray scattering and related methods have suggested that the anterior corneal stroma—extending from just beneath Bowman’s layer to a depth of roughly 100 μm—contains densely packed collagen fibrils arranged in intricate oblique interlacing patterns. These collagen lamellae also appear to exhibit a slight tilt from the central toward the peripheral cornea, a feature that may contribute not only to mechanical resistance against anterior protrusion but also to the support of active cellular metabolic processes. By contrast, the posterior corneal stroma is characterized by a looser and more nearly parallel arrangement of collagen fibrils, with less interlamellar crossing. This architecture may permit greater water content while remaining well suited to minimizing light scattering and preserving transparency. The relatively high metabolic activity of the anterior stroma likely requires continuous and efficient dissipation of internally generated entropy, including heat, metabolic by-products, and osmotic gradients. If such by-

products are not adequately removed and local thermodynamic burden accumulates, the highly ordered structure of the tissue may gradually become destabilized, potentially manifesting macroscopically as corneal edema, opacity, or structural ectasia such as keratoconus. To address this possible mechanistic gap within the classical pump-leak hypothesis, a new biophysical framework has been proposed: a “High Entropy-Production Zone (HEZ)” located in the anterior corneal stroma, together with large-scale intrastromal fluid convection arising from local interfacial physical effects associated with this zone.

Thermodynamic Basis of the High Entropy-Production Zone (HEZ) Hypothesis

The High Entropy-Production Zone (HEZ) may be conceptualized as a functional lamellar band localized at a particular depth in the anterior corneal stroma, where metabolic activity is relatively sustained. Supported by the distinctive collagen density and cellular organization of the anterior stroma, the HEZ is proposed to act as a local center of metabolic activity and associated entropy generation. From a thermodynamic perspective, one of the most important features of the HEZ is its potential to generate and maintain persistent microscale gradients. Spatially, the local entropy production rate per unit volume and time is hypothesized to reach a maximum just beneath Bowman’s layer, at a depth of approximately 50–100 μm, and then to gradually decrease toward the endothelial side. A horizontal gradient is also proposed, such that entropy production may be greatest in the central cornea near the visual axis and decrease progressively toward the peripheral limbus. To describe this biological phenomenon in mathematical terms, the present framework introduces an entropy balance relation ($\Delta S_{in} - \Delta S_{out} \leq 0$) as a guiding principle for integrating corneal metabolism, endothelial transport, and thermodynamic stability. In this formulation, entropy generated by cellular metabolic processes within the corneal stroma and endothelium—such as ATP hydrolysis, protein synthesis, and cellular respiration—must be offset by entropy discharged through the endothelial surface into the aqueous humor or through the epithelial side into the external tear environment. For the cornea to preserve its ordered and transparent state over long periods, internal entropy production would need to be continuously balanced by sufficient entropy dissipation. Within this framework, the HEZ may function as a biological engine that helps sustain thermodynamic balance. Rather than allowing metabolic

products to accumulate diffusely and irregularly, the HEZ is proposed to spatially concentrate heat and solute by-products and convert them into structured gradients. These gradients may then serve as the basis for the fluid-driving mechanism considered below.

Interfacial Physics and Marangoni-Driven Convection

The central biophysical mechanism by which the HEZ may facilitate entropy dissipation is based on interfacial fluid dynamics, particularly the Marangoni effect. The Marangoni effect refers to the generation of spontaneous flow in response to local non-uniformity in surface tension, such that fluid tends to move from regions of lower surface tension toward regions of higher surface tension. Within a hydrated porous matrix such as the corneal stroma, spatial gradients arising from the HEZ may microscopically modulate the interfacial properties of the interstitial fluid.

In the HEZ framework, this Marangoni-like behavior is separated into two interacting components

1. Thermal Marangoni Effect

Cellular metabolism inevitably produces heat. Local heat generation within the HEZ may create small temperature gradients inside the cornea. Because the surface tension of aqueous solutions generally decreases as temperature rises, the relatively warmer central anterior stroma may have slightly lower surface tension than cooler peripheral or posterior regions. In principle, such temperature-dependent surface tension differences could contribute to fluid movement from the center toward the periphery, or from anterior toward posterior regions.

2. Solutal Marangoni Effect

Metabolic activity also generates concentration gradients involving salts, dissolved gases, specific lipids, and amphipathic proteins. If metabolites with surfactant-like properties accumulate locally in the interstitial fluid, surface tension may decrease in those regions; conversely, certain salts or sugars may increase surface tension. These concentration-dependent changes may create a stronger and more spatially structured driving force for fluid flow.

An important point in support of this perspective comes from recent developments in interfacial physics. In complex biological and physicochemical

fluid systems, both theoretical and experimental work has suggested that solutal Marangoni forces can substantially exceed thermal Marangoni forces. This view is supported by advances in physical chemistry. For instance, Park et al. reported in Nature Chemistry (2023) that local ionic concentration gradients generated during the hydrogen evolution reaction produced strong solutal Marangoni forces that dominated over thermal Marangoni effects due to Joule heating, ultimately determining bubble detachment and surrounding fluid circulation. Their findings also showed that the direction of solutal Marangoni flow could vary with electrolyte composition, illustrating the strong influence of concentration gradients on fluid behavior. The HEZ model tentatively applies this physicochemical principle to ophthalmic biophysics, proposing that solute gradients generated by active metabolism in the anterior stroma may provide a major driving force for organized intrastromal fluid transport.

Strictly speaking, a pure Marangoni effect is defined as flow directly driven by surface tension gradients at a free liquid surface or a two-phase interface. The corneal stroma, however, is not a free surface but a hydrated porous tissue composed of collagen lamellae, extracellular matrix, water, and dissolved solutes. Accordingly, fluid flow within the stroma is unlikely to be governed by surface tension alone. It is more likely shaped by a combination of factors, including osmotic pressure, diffusion, stromal resistance, matrix architecture, and endothelial pump activity. For this reason, such flow may be described more appropriately as a gradient-driven transport mechanism analogous to, rather than identical with, a pure Marangoni effect.

Inoue’s Experimental Benchmark and the Conceptual AMR-DNS Framework

To move the HEZ–Marangoni hypothesis beyond a purely conceptual level, the framework was compared with a known in vivo experimental benchmark: the phenomenon of horizontal intracorneal swirling water migration described by Inoue et al. (2014) in Investigative Ophthalmology & Visual Science.

Details of Inoue’s Benchmark Phenomenon

Inoue and colleagues microinjected fluorescein into the rabbit corneal stroma and monitored fluid movement over 20 minutes by fluorescence stereomicroscopy. They observed a reproducible, time-dependent macroscopic

pattern. For approximately the first 3 minutes, the injected fluid spread linearly from the central pool toward the periphery and reached the limbus by about 4 minutes. Thereafter, the flow pattern shifted into a swirling movement along the limbal region, and by 15 to 20 minutes the tracer had spread across most of the horizontal corneal plane. This fluid behavior appeared to depend strongly on endothelial pump function. In models with endothelial injury induced by benzalkonium chloride (BAC), as well as in eyes treated with intracameral ouabain, a specific Na^+/K^+-ATPase inhibitor, the horizontal swirling pattern either disappeared or was markedly delayed. These observations suggest that active endothelial transport is closely linked to large-scale intracorneal fluid dynamics.

Adaptive Mesh Refinement Direct Numerical Simulation (AMR-DNS)

To examine whether the HEZ hypothesis could reproduce the Inoue benchmark, a conceptual in silico framework based on Adaptive Mesh Refinement Direct Numerical Simulation (AMR-DNS) was constructed. In this model, the cornea was represented as a two-dimensional horizontal slab with a diameter of 13–15 mm and a thickness of 400–450 µm, treated as an incompressible Newtonian fluid. The governing equations combined incompressible Navier–Stokes dynamics with scalar transport equations for solutes and thermal energy. To assess the relative roles and possible synergy among three physical components—the HEZ, the solutal Marangoni effect, and the thermal Marangoni effect—the simulations were divided into seven computational scenarios (Groups G1–G7). Models lacking an HEZ (G4, G5, and G7) were generally unable to generate the coherent long-range vortex-like structures needed to resemble the Inoue benchmark. Instead, they showed weak diffusive spread or rapidly decaying, competing microvortices. By contrast, models incorporating both the HEZ and the solutal Marangoni component (G1 and G2) reproduced the in vivo swirling morphology much more closely. At key time points, including 5 and 20 minutes, the G1 and G2 simulations also showed better agreement with observed spatial coverage and morphology, supporting the possibility that the solutal Marangoni effect serves as the principal driving force. In Inoue et al.’s experiment, fluorescein coverage reached 19.6% at 5 minutes and 91.8% at 20 minutes. Notably, the G1 model achieved a morphological accuracy of 96.8% at 20 minutes. These findings also suggest an additional role for heat: while the solute gradient may act as the main “locomotive,” the thermal gradient may function as a stabilizing component. In this interpretation, biological heat is not

merely waste to be removed, but may help suppress chaotic solute-driven turbulence and shape it into a more ordered, vortex-like dissipative pattern.

Optimization of Spatial Depth

Another key variable in the HEZ hypothesis is the anatomical depth at which the entropy-production layer is located. To explore this issue, a large-scale depth-sensitivity analysis was performed using the G1 model. The results suggested a functional optimum at approximately 50–100 µm beneath the corneal surface. When the HEZ was placed too superficially, for example at 25 µm, the resulting convection appeared to be dampened by viscous interaction with Bowman's layer. When it was placed too deeply, at 150 µm or more, the generated energy tended to dissipate into the looser posterior stromal matrix and became less capable of organizing large-scale vortical flow. Interestingly, the proposed optimal range of 50–100 µm corresponds closely to the region in which collagen angular dispersion and cellular density are known to peak in the anterior stroma. This may suggest that corneal architecture has evolved in a way that is particularly compatible with this type of thermodynamic transport mechanism.

The "Dual-Engine" Hypothesis of Corneal Homeostasis

When the classical pump-leak mechanism is integrated with HEZ-associated Marangoni-like convection, a broader "dual-engine" view of corneal fluid transport emerges.

The first engine is the well-established endothelial pump. This ATP-dependent mechanism maintains osmotic and electrochemical gradients across the endothelium and is essential for preventing stromal overhydration. However, active transport is metabolically costly. If the entire task of circulating and removing metabolic products across the broad horizontal extent of the cornea—13 to 15 mm in diameter—were left solely to endothelial pumps, the energetic burden on the fragile, non-regenerative endothelial monolayer might be considerable. The second engine, in this framework, is HEZ-driven Marangoni-like convection. This mechanism may be relatively energy-efficient, because it uses gradients generated by local metabolism itself as a source of fluid motion. By converting biochemical waste and metabolic heat into organized intrastromal flow, the HEZ may create a self-organized transport pathway. This swirling horizontal convection could help carry metabolic products away from the densely active central visual axis toward the peripheral limbus, thereby

reducing local entropy accumulation. This interpretation suggests a cooperative relationship: Marangoni-like convection may partly relieve the transport burden otherwise borne entirely by the endothelial pump. To describe this interaction quantitatively, the framework proposes a preliminary index termed the “Endothelial/HEZ Transport Index” (EHTI). In its classical form, the index normalizes total solute flux across the stroma by the classical Gibbs entropy production density. A high EHTI would indicate a system in which substantial transport occurs with relatively low entropy accumulation, whereas a low EHTI might suggest impaired coupling between the two transport engines. In that case, entropy would be produced but not effectively converted into organized flow, potentially contributing to local tissue degeneration or cell stress.

Extension to Quantum Thermodynamics: The Cornea as an Open Quantum System

While classical thermodynamic and fluid-dynamic models can capture many macroscopic aspects of stromal fluid transport, they may not fully account for molecular-scale and quantum-level processes occurring within the stromal matrix. To broaden the conceptual scope of the HEZ hypothesis, the framework has therefore been extended into the quantum domain by treating the cornea as an open quantum system. At the microscopic level, corneal transparency and fluid transport are shaped by interactions between water molecules and collagen, as well as by processes such as proton transfer. In many areas of quantum biology, emphasis is placed on how living systems preserve transient quantum coherence in warm, noisy environments. The HEZ framework proposes a different view: the anterior stroma may represent a region in which rapid, localized decoherence is not simply tolerated but may actually contribute to the emergence of useful macroscopic order.

von Neumann Entropy and Lindblad Dynamics

To express this model at the quantum scale, classical entropy is replaced by von Neumann entropy. In this description, the reduced density matrix represents a local quantum subsystem composed of water-collagen interactions within the HEZ. The time evolution of this subsystem, continuously coupled to surrounding thermal and solutal environmental baths, is described using a Lindblad-form Markovian master equation. Within this framework, an effective Hamiltonian couples the structural order of the HEZ to quantum dynamics through a

collagen order parameter. Lindblad operators then represent decoherence channels induced by environmental noise. In the HEZ model, these channels are assumed to be strongly influenced by local solute and temperature gradients. As these gradients become steeper, phase relaxation and energy relaxation within the water-collagen subsystem may occur more rapidly. This irreversible dissipation of quantum information can be evaluated using Spohn's inequality, which ensures consistency with the second law of thermodynamics even at the quantum level.

Cross-Scale Quantum–Classical Consistency

One of the most notable outcomes of this framework is the apparent consistency between classical fluid-dynamic simulations and quantum Lindblad-based modeling. To connect the macroscopic and microscopic descriptions, the study introduces a quantum-corrected effective surface tension in which quantum expectation values are embedded into the Marangoni shear stress term. When time-evolution simulations based on the Lindblad equation were performed, the resulting behavior closely resembled that of the classical model. This correspondence suggests that the High Entropy-Production Zone may be more than a continuum-scale artifact or a local hydrodynamic irregularity. Rather, it may represent a scale-independent dissipative structure. From this perspective, the macroscopic swirling convection observed by Inoue et al. could be interpreted as a visible manifestation of microscopic entropy dissipation and quantum decoherence translated into fluid order.

Dissipative Decoherence Structure and the Maximum Entropy Production Principle

The broader implications of the HEZ model may extend well beyond corneal physiology. If local high entropy production is not inherently destructive but instead contributes to the preservation of biological order, then the cornea may offer an especially interesting biological example of Prigogine's theory of dissipative structures. In addition, the corneal stroma may be viewed through the lens of the Maximum Entropy Production Principle (MEPP), according to which non-equilibrium systems may tend toward configurations that maximize entropy production while preserving stability. In this interpretation, the anterior stroma does not diffuse metabolic activity uniformly throughout the tissue, but instead concentrates it within a localized band—the HEZ—because this allows

the formation of steeper gradients and more effective local dissipation. These gradients then generate Marangoni-like convection, which helps remove the very by-products that created them, thereby establishing a self-sustaining cycle in which order may emerge from controlled dissipation. This concept also resonates with Stuart Kauffman’s notion of self-organization at the “edge of chaos.” Complete thermodynamic equilibrium corresponds to biological inactivity, whereas uncontrolled entropy production leads to tissue breakdown. The HEZ may represent an intermediate state in which local disorder at the microscopic level supports global order at the tissue level. In this sense, the cornea may transiently generate local “chaos” in the form of decoherence and then channel its physical consequences into the maintenance of macroscopic transparency. This perspective motivates the concept of a “Dissipative Decoherence Structure.” Unlike conventional views that treat decoherence mainly as a limitation on biological efficiency, the HEZ framework raises the possibility that biological tissues may, under some circumstances, make constructive use of continuous quantum information loss as part of a larger transport-regulation strategy. From an informational perspective, this entropy production can be seen as local information dissipation. The increase in von Neumann entropy corresponds to the process by which the cornea releases information to the external environment, and this information loss functions as the "information-theoretic cost" for maintaining transparency. In other words, corneal transparency is governed not only by mass transport and heat flux but also by "information dissipation efficiency." This point resonates with other areas of quantum biology. Whereas quantum effects in photosynthesis and olfaction are based on "coherence preservation," the corneal HEZ is unique in that it "utilizes decoherence itself for order formation". Thus, the HEZ can be proposed as a new archetype in life sciences: a "dissipative decoherence structure for maintaining order."

Clinical and Pathological Applications

An important question is whether this theoretical framework can help reinterpret clinical disease. If corneal homeostasis depends on a finely balanced dual-engine system based on entropy gradients, then several ophthalmic disorders might be reconsidered not only as structural abnormalities but also as disturbances in thermodynamic regulation and, perhaps, decoherence control.

Keratoconus and Corneal Ectasia

Keratoconus is usually understood as a biomechanical disorder characterized by progressive stromal thinning and weakening. Within the HEZ framework, however, an earlier stage of disease might also involve a localized functional failure of the HEZ itself. If solute gradients are not properly formed, or if fluid clearance becomes stagnant, metabolic by-products may accumulate in the anterior stroma. This could lead to localized entropy overload, which in turn might promote protease and matrix metalloproteinase activity and thereby contribute to collagen degradation. From this perspective, the stromal thinning seen in keratoconus might represent the macroscopic end result of a preceding microscopic thermodynamic imbalance.

Corneal Edema and Endothelial Dysfunction

Corneal edema is generally attributed to endothelial pump failure, leading to excessive stromal hydration and loss of transparency. The dual-engine hypothesis suggests a more layered mechanism. If the HEZ-associated convective engine becomes impaired, then the endothelial pump may be required to compensate for the full transport burden. Over time, such an energetic overload could accelerate depletion of ATP reserves in non-regenerative endothelial cells, promote apoptosis, and contribute to decompensation. In this view, diseases such as Fuchs' endothelial dystrophy might be influenced not only by endothelial decline itself but also by deterioration of the anterior stromal environment that normally supports passive gradient-driven transport.

Graft Rejection in Corneal Transplantation

The avascularity of the cornea is central to its relative immune privilege, yet graft rejection remains an important complication after penetrating keratoplasty, DMEK, and related procedures. If the dual-engine system becomes uncoupled through disruption of the HEZ, this may influence local immunogenicity. In the absence of efficient swirling convection capable of clearing exogenous antigens and inflammatory cytokines from the central stroma toward the limbus, such molecules may remain in place longer. Their prolonged residence time could increase the opportunity for immune recognition and inflammatory activation. In tissue-engineered corneas, the restoration or induction of HEZ-like flow patterns may therefore become a potentially meaningful therapeutic consideration for long-term graft clarity and

survival.

Next-Generation Diagnostic Biomarkers

The proposed Endothelial/HEZ Transport Index (EHTI) also suggests a possible path toward future clinical biomarkers. To make such an index clinically useful, new imaging approaches would be needed to evaluate intracorneal fluid dynamics and thermodynamic gradients in real time.

Micro-Particle Image Velocimetry (Micro-PIV): In ex vivo systems, Micro-PIV may allow direct mapping of vortex velocity fields and provide quantitative reference data for healthy and diseased corneas.

Polarization-Sensitive Optical Coherence Tomography (PS-OCT): PS-OCT may enable noninvasive assessment of depth-dependent fluid behavior and collagen angular dispersion, potentially offering indirect in vivo monitoring of HEZ integrity.

Terahertz (THz) Spectroscopy: At the quantum scale, THz spectroscopy may eventually offer a means of probing subsurface proton dynamics and water-related decoherence states, opening the possibility of measuring entropy-related processes more directly.

Low-coherence holotomography (HT), as a label-free three-dimensional imaging modality based on quantitative phase imaging and refractive-index contrast, offers volumetric visualization of biological specimens with sub-organelle resolution. In the uploaded study, HT enabled reconstruction of the 3D spatial architecture of embryos and extraction of quantitative metrics such as structural heterogeneity, nuclear organization, and blastomere arrangement. These capabilities strongly suggest that HT could be highly valuable for HEZ analysis. This is because HEZs are hypothesized to involve localized variations in structural order, hydration state, and refractive properties within tissues—features that may indirectly reflect entropy-related organizational states. HT, by

directly mapping refractive-index distributions and their heterogeneity in three dimensions, provides precisely the type of physical observables that correspond to these HEZ-associated microstructural transitions.

Effective methods for analyzing HEZ using mathematical theory

Kimura's inverse scattering field theory provides a mathematically structured framework for reconstructing the internal properties of an object from transmitted and received wave data acquired on a curved surface. In their cited work, the scattering field is formulated through a high-dimensional partial differential equation, and the internal three-dimensional image is reconstructed from boundary measurements, making the method especially suitable for computer-based and non-destructive subsurface imaging.

Qualitative methods in inverse scattering theory, including the linear sampling method and the factorization method, offer powerful ways to infer the support, shape, or boundary of a scatterer without requiring strong a priori assumptions about its material properties. These methods were developed precisely to avoid incorrect model assumptions and to extract structurally meaningful information even when only limited data are available. Their mathematical basis in functional analysis, Sobolev spaces, bounded operators, and ill-posed problems suggests that they could provide a rigorous framework for identifying the geometric or spatial signature of an HEZ-like region from indirect physical data.

These methods may contribute to HEZ analysis in complementary ways: inverse scattering field theory may help reconstruct hidden internal distributions, qualitative inverse scattering methods may help identify the spatial extent and mathematical signature of the zone.

Overall Conclusion

The integration of the High Entropy-Production Zone (HEZ) hypothesis with Marangoni-driven fluid dynamics offers a potentially important new framework for understanding corneal physiology. Rather than viewing the cornea solely through the lens of a homogeneous pump-leak model, this perspective suggests that the tissue may function as a highly organized thermodynamic system. In this view, the anterior stroma is not simply a passive structural layer, but a dynamic region in which concentrated metabolic activity generates the thermal

and solutal gradients needed to sustain organized fluid transport. The close agreement between the conceptual AMR-DNS model and the in vivo observations reported by Inoue et al. supports the possibility that intracorneal swirling convection is driven primarily by solutal Marangoni-like forces. This dual-engine model, in which passive gradient-driven convection complements ATP-dependent endothelial pumping, may reflect an especially efficient strategy for long-term maintenance of transparency in an avascular tissue. Moreover, extending this idea into a quantum thermodynamic framework using Lindblad dynamics and von Neumann entropy broadens the significance of the HEZ beyond local physiology alone. The preservation, across classical and quantum formulations, of key features such as solute dominance, thermal stabilization, and the optimal depth range of 50–100 μm suggests an intriguing form of cross-scale consistency. In this sense, macroscopic biological order may be closely linked to microscopic dissipative processes, including quantum information loss. The cornea may therefore represent a particularly compelling example of a Dissipative Decoherence Structure, in which irreversible microscopic dissipation is not merely tolerated but may contribute directly to organized macroscopic transport. By reframing tissue homeostasis as a controlled state of thermodynamic and informational dissipation, this model opens the possibility of new diagnostic concepts such as the Endothelial/HEZ Transport Index and offers fresh ways of interpreting diseases including keratoconus, corneal edema, and graft rejection. With further experimental validation using advanced imaging and biophysical measurement techniques, this framework may help clarify how the cornea sustains such a remarkable balance between local dissipation and global order.

https://doi.org/10.21203/rs.3.rs-7456650/v2
https://doi.org/10.21203/rs.3.rs-7633016/v2

This personal view proposes a new way of understanding corneal function using thermodynamic principles,
but these ideas are theoretical and not yet proven through experiments or in vivo validation.